Subject expert committees: Past, present, and future

The Central Drugs Standard Control Organization (CDSCO) plays an important role in safeguarding public health by ensuring efficacy, safety, and quality of drugs used in India. One of the important decision-making factors in the entire regulatory review process is Subject Expert Committees (SECs). A brief overview of evolution of SEC process and functioning would be helpful in further streamlining the regulatory review process.

In March 2011, the CDSCO constituted 12 New Drug Advisory Committees (NDACs),[1] consisting of experts from government medical colleges and eminent institutions within India for review of regulatory applications including new drugs, fixed-dose combinations, additional indications, and clinical trials (CTs). The review included face-to-face presentations by applicants to NDAC members in the presence of CDSCO officials. The intent of CDSCO office to initiate this step of additional review by NDAC was to protect the safety and well-being of Indian patients while ensuring strengthened regulatory environment in India.

The system of NDAC review had multiple challenges in the beginning, as expected with any new change in regulatory review system. Additional step of NDAC review led to longer review timelines. Unpredictable scheduling of NDAC meetings further delayed approval timelines. Minutes of meetings were not displayed on CDSCO website for a long time, making it less transparent regulatory review mechanism. NDAC meetings were sometimes announced a few days before the meeting date, which made it challenging for applicants to attend the meeting in person.

These 12 NDAC committees were re-named[2] as "SECs" since July 2014. It was stated in this order that the members for these committees will be drawn randomly from a large pool of experts. Later in January 2015,[3] a number of SEC panels were expanded to 25 in various therapeutic areas.

The Ministry of Health and Family Welfare has approved panels of experts of various therapeutic areas for evaluation of various categories of application of CTs/new drugs or devices for marketing in India. SEC usually comprising about eight medical experts including pharmacologists/clinical pharmacologists and medical specialists shall be constituted drawing the names of experts from respective panels. CDSCO may add names of experts from government medical college/hospitals or persons of eminence in the panels wherever considered necessary. Ideally, there needs a mechanism in place to periodically review list of SEC members ensuring no members have moved out/retired etc. The members can also be from public or private institutions.

Over a period of few years, regulators have resolved many of the teething issues of NDAC/SEC review mechanism effectively. Nowadays, there is a lot of transparency and predictability in SEC review process. SEC meeting calendar for the next 1–2 months is posted in advance on CDSCO website which enables applicants for better planning of their attendance as well as preparation. There are almost no *ad hoc* cancellations of these meetings.

Further, CDSCO in collaboration with the Indian Council of Medical Research in January 2017 published[4] a handbook for applicants and reviewers of CTs of new drugs. This handbook was supposed to enhance the quality of review of applications. It is also meant to facilitate understanding of the review process by applicants and reviewers and finally fasten approval timelines in India. Section 5.2 of this handbook describes SEC review process. It is stated that the focus of evaluation of SEC should be around various areas such as risk versus benefit, innovation versus existing therapy, unmet medical need, ethical aspects for patient safety, and India-specific concerns if any. SEC members are expected to have reviewed the application and should ask queries if any during presentation by the applicant while applicants are expected to make impactful presentation to the committee summarizing the application and answer queries if any.

As per this handbook, SEC is expected to advise the CDSCO office with thorough assessment of nonclinical data including pharmacological and toxicological data and clinical data from Phase I to IV furnished by the applicant. It was further recommended that all SEC members should be appropriately oriented on the good review practices, regulatory framework governing clinical research, and approval process in India and familiarized with the basic knowledge of Good Clinical Practices (GCPs).

Responsibilities of CDSCO representative in SEC[4] are to conduct SEC meetings not just limited to ensure that

the mandate and rules of the procedure are followed, all members have the opportunity to express their views, and ensure that scientific grounds are adequately reflected in the conclusions. It is suggested that SEC recommendation should be put on CDSCO website and provided to the applicant within 3 working days after finalization of the minutes.

Code of conduct is aptly defined in this handbook as follows:

- Members attending the SEC meeting should review the CT proposal, forwarded well in advance and submit their comments in 6 weeks
- Members must have knowledge of current CT regulations and understanding of GCP
- The overall approach of SEC panel should be scientific, rational, focused, advisory, and polite
- Recommendations should be governed by valid scientific basis and judgment
- Recommendations should be explicit and worded in an easy-to-understand language
- If the proposal does not qualify for positive opinion, clear reasons for proposed query/rejection must be provided to CDSCO.

This handbook is a great asset to ensure robust SEC review mechanism is in place in India. It is hoped that this handbook will standardize and streamline the process of evaluation and subsequent decision-making by SEC. There is some more clarity needed in some areas in the next version of this handbook, while in some areas, robust implementation of the existing guidance is desirable.

Further, defining the exact scope of review of Clinical Trial Application/New Drug Application (NDA) which means clarifying areas which are out of scope of SEC review, for example, pricing, access strategy of NDA, investigator sites selection, etc., to avoid confrontations by applicants. It is observed that all the applications of new drug, new strength, additional/expansion of existing approved indication/package insert approval, protocol amendments, or extension studies of already approved CTs are also referred for SEC review. It is usually a topic of debate in public forums which categories applications should be referred for SEC review. It would be greatly beneficial, if in the next version of this handbook, an additional clarity is provided about categories of applications to be referred for SEC review. Further, there appears a need to expand SEC panels to include experts from wider therapeutic areas. In this regard, notice[5] was issued by CDSCO in November 2017 inviting applications for inclusion in SECs from professionals of expanded areas such as biostatistician, cell-and-cell-based therapy, gene therapy, biomedical engineering, phytopharmaceuticals, toxicology, and veterinary sciences.

Further, it is observed that many a times, there is nonuniformity in the review by SECs in different therapeutic areas. There is considerable heterogeneity in the minutes of different SECs with almost no insight into the process of decision-making. Some more guidance is also desired for decision-making on granting CT waiver for new drug approval. There is considerable variability in minutes, and details are not adequate, making it difficult to get insights into decision-making process. Implementation of the said handbook and formation of more specific standard operating procedures or guidance document may help bring more uniformity across therapeutic areas.

In the issue of this journal, an article by Shetty *et al.*[6] reflects the analysis of SEC meetings conducted during the period of July 1, 2014–October 31, 2017, and minutes accessed from CDSCO website. The said audit included a total of 317 SEC meetings with 2616 agenda items. Considerable variability was seen during the analysis. Applications seeking marketing authorization with CT waiver were 5 times more likely to be rejected than applications not seeking such waiver. This also implies that guidelines for local CT waiver need to be more defined in future. Applications in oncology were granted CT waiver 6.5 times more often than nononcology. Interesting finding was also that majority (~92%) of CT applications receive approval, and very few were rejected by SECs. Overall, considerable variability was observed in meetings of different therapeutic areas, and there appears a need to bring more uniformity in decision-making process.

Similar advisory panels exist in offices of major regulators worldwide such as the United States Food and Drug Administration (US FDA) and European Medicines Agency as well. It is interesting to know their way of functioning, norms of selection, and composition of such panels in major countries.

The purpose of Oncology Drug Advisory Committee (ODAC) in the United States[7] is to review and evaluate data concerning the safety and effectiveness of marketed and investigational human drug products for the treatment of cancer. ODAC is expected to make appropriate recommendation to US FDA commissioner. ODAC consists of a core of 13 voting members including the chair. Members and the chair are selected based on the knowledge in the field of general oncology, hematologic oncology, pediatric oncology, immunologic oncology, and

biostatistics. ODAC receives requests for technical and clinical evaluation of new drugs by the US FDA. The committee makes nonblinding recommendations to both the Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research divisions of the US FDA about approving new drugs to treat cancer.[8] Unlike Indian regulatory review mechanism, ODAC review is not mandatory for all new product approvals. ODAC review meeting is convened only at the request of US FDA if the matter is of significant public interest and obtaining advice is beneficial or matter is controversial, for example, FDA reviewers have differences of opinion during the review, or risk-benefit ratio is not straightforward or significant safety concerns or questions about the use of product in certain subpopulation. Statistics of oncology approvals granted by the US FDA involving ODAC review is interesting. Out of all oncology new drugs approved by the US FDA, very few were sent to ODAC for opinion, which indicates that not all applications are referred to ODAC for expert review. ODAC is usually not convened to discuss CTs which are submitted to the IND, annual safety label updates, and new formulations. ODAC meeting is between scientific experts, US FDA, and the applicant and is open to public viewing. In EU, there exist similar advisory committee terms as Scientific Advisory Group-Oncology (SAG-O)[9] which functions in similar manner.

In conclusion, it is always beneficial to have subject matter experts' advisory to regulators to protect patient safety and well-being. Clinical expertise added with real-life experiences may add a lot of value in clinical judgment and may help decision-making process. Such review mechanism needs to categorize types of applications that need advice, adequate-controlled occurrence of such meetings, fair chance of presentation to the applicant, and unbiased review by members. Sharing of best practices of conducting such advisory mechanism in different countries will benefit regulators worldwide to further streamline and strengthen such reviews to ensure early access of right drug to the right patient.

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